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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/804,950	03/19/2004	Christine Konradi	04843/120003	8080

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EXAMINER	
SALMON, KATHERINE D	
ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
12/10/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/804,950	KONRADI ET AL.	
	Examiner	Art Unit	
	KATHERINE SALMON	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 39-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 39-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to papers filed 9/09/2009.

2. Currently Claims 1-2 and 39-41 are pending. Claims 3-38 have been cancelled.

3. The following rejections are reiterated. Response to Arguments follows.

4. It is noted that the petition of 7/31/2009 has been granted (9/04/2009) and therefore the finality of the last office action (7/09/2009) has been withdrawn.

5. This action is FINAL.

Withdrawn Objections

6. The objection to claim 2 made in section 8 of 7/31/2009 has been withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not

commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1, 39-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van den Heuvel et al. (American Journal Human Genetics 1998 Vol 62 p. 262) in view of Lockhart et al. (US Patent 6040138 March 21, 2000).

With regard to Claim 1, Van den Heuvel et al. teaches a mutation in the human nuclear gene encoding the AQDQ subunit of the mitochondrial respiratory chain complex I (abstract). Van den Heuvel et al discloses the cDNA sequences of the nuclear gene which results in the mutation (p. 263 1st column 3rd paragraph). Therefore Van den Heuvel et al. teaches nucleic acids molecules which encode the polypeptides of complex I of the mitochondrial respiratory chain being naturally coded for by a nuclear gene. Van den Heuvel et al. teaches the use of only nuclear genes to detect a pathogenic mutation in a population which caused enzyme deficiency (p. 262 1st column 1st paragraph).

However Van den Heuvel et al. does not teach placing the nucleic acid fragments of the mutation onto a microarray.

With regard to Claim 1, Lockhart et al. teaches placing oligonucleotides probes onto an array (solid support) to detect expression (Abstract).

With regard to Claim 39, Lockhart et al. teaches the probes can be at least 40

nucleotides in length (column 15 lines 53-60).

With regard to Claims 40-41, Lockhart et al. teaches that the array of probes can comprise up to 100 different oligonucleotide probes (abstract).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to bind the nuclear gene associated with the mutations taught by Van den Heuvel to the array taught by Lockhart et al. with a reasonable expectation of success. The ordinary artisan would want to incorporate the nuclear gene associated with mutations onto the array because Lockhart et al. teaches that probes on an array can be used to detect a large number of different target nucleic acids at once and determine the relative abundance of each in a sample (Column 2 lines 35-55). Therefore the ordinary artisan would be motivated have an array consisting of only the nuclear gene associated with the mutation taught by Van den Heuvel in order to detect the mutation in a number of patients simultaneously.

Response to Arguments

The reply traverses the rejection. A summary of the arguments presented in the reply is provided below with response to arguments following.

The reply asserts that the applicants have discovered that subject having bipolar disorder exhibit reduced expression of nuclear genes encoding polypeptides of complexes I-V of the mitochondrial respiratory chain (p. 2 last paragraph). The reply asserts that the array is directed to a composition consisting of 90% nucleic acids which

are nuclear encoded genes which would result in the exclusion or omission of mitochondrial encoded genes from the array (p. 3 1st paragraph). The reply asserts that the references cited are directed to analysis of mitochondrial function and general (p. 3 2nd paragraph). The reply asserts that the array of the references would include other mitochondrial genes which focus on mitochondrial function and not the claimed nuclear encoded genes.

The reply asserts that Van den Heuvel does not teach the use of only nuclear genes, but rather is focused on the identification of mutations that result in complex I deficiency, be they nuclear or mitochondrial in origin (p. 3 last paragraph). The reply points to p. 262 of Van den Heuvel and notes that complex I includes more than 41 subunits of which 7 are encoded by the mitochondrial genome (p. 3 last paragraph). The reply asserts that while Van den Heuvel describes the identification of a specific mutation in the AQDQ subunit of complex I there is no suggestion to exam only this particular gene or to exam only nuclear encoded genes of complex I (p. 4 1st paragraph).

These arguments have been fully considered but have not been found persuasive.

The claimed microarray consists of known nuclear genes. Van den Heuvel et al. Teaches that the nuclear genes of complex one are associated with a mutation to detect a pathogenic mutation. Therefore it is know to one of ordinary skill in the art at the time of filing a reason to detect nuclear genes such as the nuclear gene in complex I as taught by Van den Heuvel et al. grammar Although it is acknowledged that there are

mitochondrial genes in the complex, the teachings of Van den Heuvel are specific to mutations within the nuclear gene encoding the AQDQ subunit. As taught by Lockhart et al. it is well within the knowledge of the ordinary artisan to place any number of nucleic acids onto an array. Herein in this specific case it would have been obvious to place probes which detect the specific mutation of the AQDQ subunit onto an array. Lockhart et al. teaches that the array of probes can comprise up to 100 different oligonucleotides probes. In this case it would have been obvious to the ordinary artisan to incorporate only probes associated with the specific mutations onto the array. As such the array would be limited to only nuclear genes. Therefore although the complex I might include mitochondrial genes, the mutations detected by the art would be encompassed only in the nuclear genes. The art teaches the ordinary artisan to make any number of different combinations of probes onto an array. Therefore the combination of references suggests that array can consist of only the nuclear genes.

12. Claims 1-2, 39-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace et al. (US Patent Application Publication US 2006/0099578 May 11, 2006) as evidenced by Wallace (US Patent 5494794 February 27, 1996, referred to as Wallace '794) in view of Van den Heuvel and Smeitink (Bioessays 2001 VOl. 23 p. 518) and Papaconstantinou et al. (US Patent Application publication 2008/0187911 August 7, 2008 priority to 1/30/2003).

With regard to Claim 1, Wallace et al. teaches microarray consisting of probes for mitochondrial genes (abstract). Wallace et al. teaches that these arrays can contain

subsets of probes drawn to mitochondrial energy (p. 2 paragraph 10). Wallace et al. teaches that the microarray can be composed of mtDNA genes from NADH, Cytochrome b, Cytochrome c, ATP synthase 6, ATP synthase 8 (Table 1 and p. 3 paragraph 17). Therefore Wallace et al. teaches a microarray comprising nucleic acid molecules that encode polypeptides of complex I, II, III, IV, or V (e.g. NADH, Cytochrome b, Cytochrome c, ATP synthase 6, ATP synthase 8). Wallace et al. teaches that the arrays can be designed such that genes related to OXPHOS are detected (p. 9 paragraph 64).

OXPHOS is composed of 5 enzyme complexes assembled from 13 mitochondrial DNA and 50 nuclear DNA subunits (as evidenced by Wallace '794 Column 1 lines 60-67). Wallace '794 teaches that OXPHOS is composed of Complex I (NADH); complex III (cytochrome c and cytochrome b); Complex IV (cytochrome c, COI, COII, COIII); and complex V (ATP synthase) (as evidenced by Wallace '794 Column 1 lines 60-67 and Column 2 lines 1-5). Therefore an array related to OXPHOS would include nucleic acid molecules of mitochondrial respiratory chain of complex I, III, IV, and V.

With regard to Claim 2, Wallace et al. teaches the array can include any number of genes related to mitochondrial function including ATP Synthase, F1 complex, 0 subunit; ATP Synthase, F0 complex, d subunit; ATP Synthase, F0 complex, C3 subunit; ATP Synthase, F1 complex, gamma polypeptide 1; ATP Synthase F0 complex subunit F (Table 3).

With regard to Claim 39, Wallace et al. teaches that the probes are 20-30 nucleotides in length (p. 4 paragraph 24).

With regard to Claims 40-41, Wallace et al. teaches the microarray can contain probes for all genes involved in mitochondrial biology or can contain probes for at least 10 genes or at least 25 genes (p. 6 paragraph 42).

However, Wallace et al. does not teach a microarray which consists of only nucleic genes of the mitochondrial respiratory chain.

With regard to Claim 1, Van den Heuvel and Smeitink teach although deficiencies can be either the mitochondrial DNA or nuclear DNA, the percentage of those patients with mitochondrial DNA abnormalities is relatively low (p. 518 2nd column 1st full paragraph). Van den Heuvel and Smeitink teaches that therefore screening for common mtDNA mutations in patients with established OXPHOS disorder (ATP through oxidative phosphorylation) is unsatisfactory (p. 518 2nd column 1st full paragraph). Therefore Van den Heuvel and Smeitink teach that it would be useful to screen for abnormalities in nuclear DNA.

Papaconstantinou et al. teaches microarrays of nucleic encoded genes (paragraph 120 p. 20). Papaconstantinou et al. teaches that the microarray for detection of a particular invention can be composes solely of gene of nuclear origin wherein the genes encoded by the mitochondrial DNA were removed (paragraph 126 p. 24). Therefore Papaconstantinou et al. teaches that micorarrays can be designed such that only nuclear genes are detected.

Therefore it would be prima facie obvious to one of ordinary skill in the art to modify the various subsets of microarrays taught by Wallace et al. to design an array consisting of at least 90% nuclear genes for the use of detection of nuclear

abnormalities as taught by Van den Heuvel and Smeitink. The ordinary artisan would be motivated to design an array of only nuclear genes because Van den Heuvel and Smeitink teach that the vast majority of abnormalities are from nuclear DNA. Further Papaconstantinou et al. teaches that that the ordinary artisan would be able to design microarrays consisting only of nuclear genes. It would have been obvious to one of ordinary skill in the art at the time the invention was made to design an array only of nuclear genes with a predictable expectation of successful screening of diseases associated with nuclear genes. The ordinary artisan would be motivated to produce an array consisting of only nuclear genes because Van den Heuvel and Smeitink teach that the majority of mutations are associated with nuclear genes.

Response to Arguments

The reply traverses the rejection. A summary of the arguments presented in the reply is provided below with response to arguments following.

The reply asserts that the primary'578 reference teaches arrays useful for studying mitochondrial function (p. 4 last paragraph). The arrays of the '578 reference comprises both nuclear and mitochondrial genes and therefore there is no disclosure of any array where at least 90% of the nucleic acids molecules are nuclear encoded genes (p. 4 last paragraph). The reply assert that there is no reason provided to exclude the mitochondrial genes from the '578 array (p. 4 last paragraph). The reply assert that Smeitink et al does not teach that mtDNA mutations should be ignored, but rather the frequency of patients with mtDNA is relatively low (p. 5 1st paragraph). The reply

asserts that '911 reference asserts that the disclosed arrays should encompass all the factors that will affect mitochondrial biogenesis and assembly and mitochondrial function (p. 5 2nd full paragraph). The reply asserts that the office action points to example 3 of '911 showing the removal of 13 mtDNA genes from the arrays containing nuclear encoded genes (p. 5 last paragraph). The reply asserts that this teaching in '911 does not suggest the claimed invention as the mtDNA genes were analyzed on a separate array.

These arguments have been fully considered but have not been found persuasive.

Although none of the cited art specifically teaches an array consisting of only 90% nuclear genes, the cited prior art in combination suggest the structure of such an array. Wallace et al. teaches construction of an array comprising nuclear and mitochondrial genes. Van den Heuvel and Smeitink teach that the majority of abnormalities are from nuclear DNA. Therefore is would be obvious to design arrays which comprise nuclear genes. Although Papaconstantinou et al. teaches that arrays can comprise nuclear and mitochondrial genes, Papaconstantinou et al. specifically teaches that these two sets of gene types can be on separate arrays. The reply acknowledges that Papaconstantinou et al. teaches analysis of mtDNA genes on a separate array. Herein in the instant case it would be obvious to the ordinary artisan to design any number of arrays which compose nuclear genes, including an array consisting of 90% nuclear genes. These genes are known in the art and are known to have associations to specific disease (see Van den Heuvel and Smeitink). The art

further teaches that different combinations of probes can be placed on an array structure depending on what the array is used for. Papaconstantinou et al. teaches that an array can be designed for nuclear genes and an array can be designed for mitochondrial genes. As such the art suggest arrays consisting of known nuclear genes. The reply has not provided any evidence that such a structure would be unpredictable based on the teachings in the art. These components on the array (e.g. the nuclear genes) are known in the art and have been shown in the art to be associated with particular abnormalities. The art teaches that arrays can be designed which encompass various combinations of nuclear and mitochondrial genes (including in Example 3 of Papaconstantinou et al. an nuclear array which has the mitochondrial DNA removed). Therefore the combination suggests the structure claimed.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHERINE SALMON whose telephone number is (571)272-3316. The examiner can normally be reached on Monday - Friday 9AM-530PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Katherine Salmon

/Sarae Bausch/
Primary Examiner, Art Unit 1634